Int Clin Neurosci J. 2025;12:e5 Case Report

doi: 10.22037/icnj.v12i1.50806

FOXG1 Syndrome: Unraveling Congenital Rett-Like Disorder

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Abstract

FOXG1 syndrome is a rare neurodevelopmental disorder caused by mutations in the *FOXG1* gene, leading to severe developmental delay, microcephaly, movement disorders, epilepsy, and autistic features. Though it shares some phenotypic similarities with Rett syndrome, it has a distinct genetic etiology and clinical course. We report a 1-year-old 3-month-old boy, the second-born child of a non-consanguineous couple, who presented with recurrent seizures from 4 months of age, characterized by infantile spasms. The child exhibited global developmental delay, poor social interaction, irritability, and sleep disturbances. Clinical examination revealed microcephaly, hypotonia, exaggerated deep tendon reflexes, and extensor plantar responses. Neuroimaging showed benign enlargement of the subarachnoid space, and genetic testing confirmed a pathogenic *FOXG1* mutation. Despite multiple anti-seizure medications, the child's epilepsy remained refractory. He is currently being managed on a ketogenic diet, anti-epileptic medication, and intensive multidisciplinary therapy sessions. This case highlights the diagnostic challenges of FOXG1 syndrome and its overlapping but distinct features from Rett syndrome. The patient's refractory epilepsy, severe developmental delay, and poor response to conventional therapies align with existing literature. Neuroimaging findings in these patients are varied. This syndrome has a poor prognosis, with no definitive treatment available at present. FOXG1 syndrome is a distinct entity requiring early diagnosis and multidisciplinary management. Further research into gene-targeted therapies is crucial for improving outcomes.

Keywords: FOXG1 gene mutation; developmental delay; Congenital Rett-Like Disorder; neurodevelopmental disorder.

Received: November 07, 2025, **Accepted:** December 19, 2025, **Published online:** May 05, 2026

Citation: Balakumaran P, Daniel NJ, Rajan N, Kumar PP. FOXG1 Syndrome: Unraveling Congenital Rett-Like Disorder. Int Clin Neurosci J. 2025;12:e5.

Introduction

FOXG1 syndrome is a rare neurodevelopmental disorder caused by mutations in the Forkhead box G1 (FOXG1) gene located on chromosome 14q12. Since its description in 2008, it has gained recognition as a distinct disorder due to advances in genetic testing, particularly whole exome sequencing (WES).[1] The syndrome is characterized by severe global developmental delay, intellectual disability, early-onset epilepsy, stereotypy, and movement disorders. It shares some clinical similarities with Rett syndrome but differs in its genetic etiology and presentation, notably lacking an initial period of normal development.[2]

Seizures, particularly infantile spasms, are a hallmark feature of FOXG1 syndrome, often resistant to conventional anti-seizure medications, making management challenging.[3] Affected children frequently exhibit hypotonia, irritability, poor eye contact, sleep disturbances, and impaired social skills. Neuroimaging findings, such as corpus callosum abnormalities and a simplified gyral pattern, may aid in diagnosis.[4]

The investigation of choice for confirming FOXG1 syndrome is molecular genetic testing, including gene panels or whole exome sequencing (WES).[5] However, treatment remains symptomatic, focusing on seizure control, developmental support, and improving the quality of life. A multidisciplinary approach, involving neurology, physiotherapy, occupational therapy, and speech therapy, is essential for optimizing outcomes.[6] Early intervention plays a crucial role in enhancing motor, social, and communicative abilities.[7]

Here, we present a 1-year-old and a 3-month-old child diagnosed with FOXG1 syndrome, highlighting the challenges in seizure management and the importance of multidisciplinary care in improving the child's prognosis.

Case Report

Clinical description

A 1-year-old 3-month-old male child, second-born to a non-consanguineous couple, presented with recurrent seizures since 4 months of age. He was delivered via normal vaginal delivery, with a birth weight of 3 kg, cried immediately after

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birth, and had no postnatal complications. There is no significant family history (Figure 1).

Seizures began as infantile spasms occurring in clusters, accompanied by global developmental delay. At present, he has attained head control, unidextrous grasp, cooing, and a social smile, corresponding to a developmental age of 4 months. Additional concerns include prolonged irritability, sleep disturbances, poor eye contact, and impaired social interactions.

On examination, he had a prominent forehead, sutural overriding, and microcephaly (head circumference: 42 cm; Z score < -3). His weight was 11.2 kg (0 to +1 SD) and his length was 80 cm (0 to +1 SD). He had mild hypotonia in all 4 limbs, exaggerated deep tendon reflexes, and bilaterally extensor plantar reflexes. Other system examinations were unremarkable.

During subsequent follow-ups, the child was found to have stereotypical and hyperkinetic movements when seizure-free.

Management & Outcome

MRI brain revealed benign enlargement of the subarachnoid space of infancy. Whole exome sequencing confirmed a pathogenic FOXG1 mutation. Though the EEG done under sedation did not reveal any abnormality, the child was clinically diagnosed to have infantile spasms.

Seizures remained refractory despite multiple anti-seizure medications, including sodium valproate, vigabatrin, clobazam, and zonisamide. Steroid therapy was ineffective. A ketogenic diet was initiated. The child is currently on sodium valproate, zonisamide, melatonin, and clobazam, along with regular physiotherapy, speech, and occupational therapy.

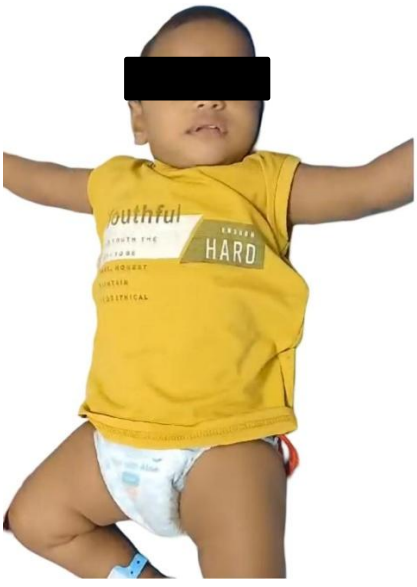

Figure 1. Child with prominent forehead with sutural overriding, microcephaly (head circumference: 42 cm, < -3 Z score.

Currently, he experiences one seizure per day. While seizure frequency has reduced with medication, they persist periodically. The child also has a severe intellectual disability (IQ: 20-30%).

Discussion

FOXG1 syndrome is a severe neurodevelopmental disorder characterized by global developmental delay, microcephaly, epilepsy, movement disorders, and autistic traits. The present case demonstrates many hallmark features, including early-onset epilepsy (infantile spasms), severe developmental delay, hypotonia, poor social interaction, and treatment-resistant seizures. The child's heterozygous pathogenic FOXG1 variant is consistent with previously reported cases.[1,2]

Infantile spasms, as seen in this case, are a common presentation of FOXG1 syndrome. Vegas et al.[4] reported that 67% of patients with FOXG1 syndrome develop epilepsy, with infantile spasms being the most frequent type. Seizures are often drug-resistant, as seen in our patient, who had a limited response to sodium valproate, vigabatrin, clobazam, and zonisamide. Similarly, Striano et al.[5] highlighted the refractory nature of seizures, suggesting the need for alternative therapies such as the ketogenic diet. Our patient was initiated on a ketogenic diet; however, non-compliance was an issue. The ketogenic diet has shown promise in reducing seizure frequency in FOXG1 syndrome, as noted by Paciorkowski et al.[7]

The MRI findings in our patient revealed benign enlargement of the subarachnoid spaces. This finding has been described in some neurodevelopmental disorders, but is not a defining feature of FOXG1 syndrome.[3] In contrast, Vegas et al.[4] analysed 45 patients and found that frontal pachygyria, simplified gyration, and corpus callosum hypogenesis were the most characteristic MRI findings. This suggests variability in neuroimaging presentations, potentially influenced by mutation type. Frameshift and nonsense mutations in the N-terminal FOXG1 region, as observed in our case, are associated with more severe neuroimaging abnormalities and worse clinical outcomes.[4,8]

The child in our case had severe intellectual disability (IQ 20–30), poor eye contact, irritability, and sleep disturbances, aligning with Wong et al.[8], who found that 51% of FOXG1 patients suffer from significant sleep disturbances. Our patient exhibited autism spectrum traits, a common feature of FOXG1 syndrome. Mueller et al.[9] conducted a meta-analysis on over 36,000 pediatric patients with neurodevelopmental disorders, confirming that FOXG1 mutations contribute to a distinct syndromic form of autism, with MECP2 and CDKL5 mutations being more prevalent.

A striking observation in our case was the severity of irritability and prolonged crying spells, which have been underreported in FOXG1 literature. Tully & Dobyns[10] suggested that these behaviours might be linked to dysfunctional GABAergic signalling in FOXG1 syndrome.

The hyperkinetic movement disorder seen in FOXG1 syndrome, comprising chorea, dystonia, and stereotypies, was present in our patient and has been well-documented in prior studies.[4,8]

The type of FOXG1 mutation plays a crucial role in the severity of the phenotype. Though our patient did not have any major structural neurological abnormality, there are reports of the same heterozygous pathogenic variant with frameshift and nonsense mutations in the N-terminal region resulting in severe motor impairment, profound intellectual disability, and cortical malformations.[4,8] Conversely, missense mutations tend to have milder neurodevelopmental consequences.[2] These findings underscore the importance of genotype-phenotype correlations for prognosis and genetic counselling.

Multidisciplinary care is essential for FOXG1 syndrome. Our patient is receiving physiotherapy, occupational therapy, and speech therapy, similar to recommendations by Paciorkowski et al.[7], who emphasized that early intervention significantly impacts motor and cognitive function. However, the prognosis remains poor, with most patients requiring lifelong care and support.[1,2]

This case reinforces existing literature on FOXG1 syndrome, particularly in the context of epilepsy and neurodevelopmental impairment. It also highlights the challenge of seizure control and the need for alternative therapies such as the ketogenic diet and behavioural interventions for irritability and sleep disturbances. Continued research is needed to explore targeted molecular therapies that could improve long-term outcomes.

Conclusion

FOXG1 syndrome and Rett syndrome share some clinical similarities, but they are distinct disorders with different genetic causes, developmental trajectories, and phenotypic manifestations. Early diagnosis, multidisciplinary care, and continued research into targeted therapies are essential for improving outcomes in FOXG1 syndrome.

Acknowledgments

None.

Competing Interests

The authors declare no conflict of interest.

Funding

None.

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